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All *trans*-Retinoic Acid Decreases Early Mortality in Patients With Promyelocytic Leukemia and Can Be Given Entirely on an Outpatient Basis

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The results of the treatment of 43 patients with acute promyelocytic leukemia (PML) are reported: 27 were treated initially with all-*trans*-retinoic acid (ATRA), whereas 16 were treated with conventional chemotherapy. All patients received myelosuppressive chemotherapy after the initial treatment. Respectively, the complete remission rate was 92% and 37% ($P < 0.01$), the 5-day mortality rate was 0% and 44% ($P < 0.001$), and the 28-day mortality rate was 4% and 44% ($P < 0.001$). The median disease-free survival was 12 and 1 months ($P < 0.01$), whereas the 12-month disease-free survival was 50% and 13% ($P < 0.01$) and the 36-month disease-free survival was 41% and 9% ($P < 0.01$). Thirteen of the patients treated with ATRA were given the treatment fully as outpatients. ATRA given as initial therapy decreased significantly early mortality in promyelocytic leukemia patients; because some promyelocytic leukemia patients given ATRA as initial therapy can be treated as outpatients, the costs of this treatment modality may be diminished. Am. J. Hematol. 62:139–143, 1999.

Key words: leukemia; promyelocytic; ATRA; mortality; outpatient

INTRODUCTION

Acute promyelocytic leukemia (PML), the M-3 variant of the FAB classification, is characterized by a reciprocal and balanced t [15,17] translocation with a gene rearrangement that fuses the retinoic acid receptor alpha (RAR-α) gene with a putative transcription factor PML gene [1]; this chimerical PML/RAR-α gene encodes a functionally altered retinoid acid receptor [2–5]. Reverse-transcriptase polymerase chain reaction (RT-PCR) techniques are useful in the detection of PML/RAR-α messenger RNA (mRNA) for diagnosis, follow-up and the study of residual disease after treatment [4–8]. PML is exquisitely sensitive to the administration of supraphysiological amounts of all-*trans* retinoic acid (ATRA): most patients with PML achieve complete remission when given ATRA solely [7–8]. Only PML patients displaying the PML/RAR-α mRNA are responsive to ATRA [5–8]. ATRA-induced complete remissions (CR) in PML are short and frequently PML/RAR-α (+) [4,6,8], and myelosuppressive chemotherapy (CT) supported or not by either bone marrow (BM) or peripheral blood stem cell grafts may render molecular remissions, which are associated with longer disease-free survivals (DFS) [4,6–9].

PML is more frequent in Mexican mestizos than in Caucasians [10–11], and prospective studies in our country to asses the results of treatment of PML patients with ATRA have been conducted and reported preliminarily [12]. We analyze here the results obtained in the treatment of a group of 43 patients with PML; 27 of them were treated initially with ATRA, whereas 16 of them

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received combined CT as front-line therapy. Thirteen of the 27 patients given ATRA as front-line therapy were treated completely as outpatients.

MATERIAL AND METHODS

Patients

All consecutive patients with PML studied and treated in the Centro de Hematología y Medicina Interna de Puebla (Puebla, México), the Hospital Universitario (Puebla, México), the Centro Médico de Occidente (Guadalajara, México), and the Hospital Universitario de Monterrey (Monterrey, México) were prospectively entered in the study from March 1991 to March 1998.

Diagnosis

Peripheral blood and BM smears stained with May Greenwald Giemsa were studied and the classification was performed according to the FAB classification [13]. The immunophenotype of the malignant cells was analyzed by means of flow cytometry [14–15]. By means of RT-PCR, the PML/RAR-α fusion gene was investigated [17] at diagnosis and along the treatment.

Treatment

Arm A. Patients were started in ATRA (Hoffman-La Roche AG, Nutley, NJ) 45 mg/m^2 po, daily together with prednisone (50 mg/m^2 po, daily during 21 days), before any treatment, at the time of diagnosis. ATRA and prednisone were given on an outpatient basis in patients fully active, able to stay in their houses, with relatives or friends or in nearby-hotels, a fair educational level, and able to visit the clinic every day. If the white blood cell count (WBC) raised above 30 × 10 m^9/l, ATRA was reduced to 20 mg/m^2 po, and intravenous myelosuppressive CT in one or two doses (cyclophosphamide or cytarabine) was delivered until achieving 10 × 10 m^9/l WBC. ATRA was given until reaching a complete hematological remission, as defined by usual criteria [13]. Two weeks after achieving CR, a combined 7 + 3 CT course by using cytarabine and doxyrubicin (cytarabine 100 mg/m^2 in infusion for 7 days and doxyrubicin 45 mg/m^2 in bolus for 3 days) [18] was delivered, on an outpatient basis. Once the blood cell counts had recovered, an autologous peripheral blood stem-cell autotransplant was performed in some patients, whereas in the rest of the patients an additional course of 5 + 2 CT was given. At this point, patients were allocated to receive "continuation" therapy with oral daily mercaptopurine (50 mg/m^2) and oral weekly methotrexate (25 mg/m^2) [13] until completing 12 months from the start of treatment. Patients for whom ATRA was not available were allocated to arm B.

Arm B. A combined CT course by using cytarabine and doxyrubicin or mitoxantrone during 7 and 3 days, respectively (7 + 3), as mentioned previously [18] was delivered, on an outpatient basis when feasible. Two weeks after achieving CR, another combined CT that uses cytarabine and doxyrubicin or mitoxantrone in identical doses during 5 and 2 days, respectively (7 + 3) was delivered, also as outpatients. Patients were then allocated to receive "continuation" therapy with oral daily mercaptopurine and oral weekly methotrexate (vide supra) until completing 12 months from the start of treatment.

RESULTS

Forty three patients were accrued: 27 could be given ATRA and 16 were given CT as front-line therapy. The median age of all the group was 30 years, range 8–56; there were 27 females. The chimerical PML/RAR-α gene was shown in 12 patients at diagnosis, whereas the caryotype showed the 15:17 translocation in 10. In 21 the diagnosis was done solely on morphologic and cytochemical basis (19 patients in arm A and 2 patients in arm B). Seven patients exited early due to death within the first 5 days of treatment; all of them were being treated with CT ($P < 0.001$).

Arm A. The median age of the patients in this group was 31 years (range 8–56). A complete remission was obtained in 25 of 27 patients (92%); the two patients that showed no response were not tested for the PML/RAR-α gene nor the 15:17 translocation. The median time of administration of ATRA in order to achieve the CR was 2 months. Thirteen patients were given ATRA fully as outpatients. Fourteen patients were treated at the hospital because they were unable to stay in hotels or in nearby houses. Five patients developed a WBC above 30 × 10^9/l, fever, and mild dyspnea; accordingly, they were given both intravenous steroids and chemotherapy; there were no instances of full-blown ATRA syndrome. A cytogenetic and/or molecular remission was obtained in 83% of patients tested after the initial course of ATRA. Three of the 25 patients who achieved a CR died during hypoplasia induced by the consolidation CT, one died due to cranial trauma and the other of congestive heart failure. Of the remaining 20 patients that went into a CR, 6 (30%) relapsed at intervals from 8 to 50 months. Three patients received an autologous, nonfrozen, nonpurged peripheral blood stem cell autograft [4,6,9,19]. The median survival in this arm was 12 months (range 1–70), the 12-month DFS was 50%, the 36-month DFS was 41% and the 5-year DFS was 9%. Figure 1 shows the Kaplan-Meier [20] survival plot of these patients.

Arm B. The median age of the patients in this group was 27 years (range 17–51). All patients were hospitalized during the continous infusion of cytarabine. Seven patients exited early due to death within the first 5 days of treatment; this contrasts with the early mortality of the

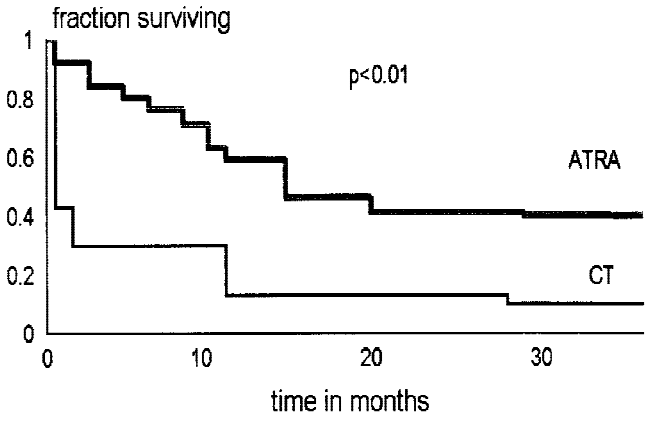

Fig. 1. Survival plots according to Kaplan and Meier (20) of the 43 patients with promyelocytic leukemia treated initially with all trans-retinoic acid (ATRA, n = 27) or combined chemotherapy (CT, n = 16). All patients received myelosuppresive CT after the initial treatment.

patients treated in arm A, which was 0%, ($P < 0.001$). A CR remission was obtained in 6 of 16 patients (37.5%) and in 6 of 9 (66%) of those who received at least one complete course of combined CT. The patients who achieved a CR in this arm were not tested for the cytogenetic or the molecular marker of the disease. Four of the 6 patients who achieved a CR died during the consolidation CT. Of the remaining 2 patients, one relapsed at 20 months. The median SV of these patients was 1 month (range 0.5–84), the 12-month DFS was 13%, the 36-months DFS was 9% and the 5-year DFS was 2%. Figure 1 shows the Kaplan-Meier [20] survival plot of these patients. There were no significant differences between arms A and B of treatment as far as the WBC (10.8 vs. 12.2 $\times 10^9$/l), platelet count (48.6 vs. 39.8 $\times 10^9$/l), fibrinogen levels or D-D dimers are concerned; however, when comparing patients who died early with those who survived, there were differences in both WBC and platelet count: patients who died early had higher WBC at diagnosis (17.3 vs. 3.0 $\times 10^9$/l) and lower platelet counts at diagnosis (25.9 vs. 70.6 $\times 10^9$/l), $P < 0.01$.

DISCUSSION

In the last 6 years major advances have occurred in PML. Until recently, most centers grouped PML with other subtypes of AML, and patients were treated with a combination of an anthracycline and cytosine arabinoside for remission induction [21]. Twelve years ago, the first patients with PML were treated with ATRA [22]. By now, combined data from China, France, United States of America, Japan, and other countries indicate that the mean CR response rate consistently approximates 85% [6,8,12,21–23]; accordingly, induction to remission in PML by using ATRA is now the front-line therapy in this peculiar type of leukemia. Nevertheless, remissions induced and maintained solely by ATRA are rather brief in duration [8,21–23], the median duration of remission in the New York series being 3.5 months (range 1–23 months) [23]; accordingly patients who achieve a CR with ATRA should receive cytotoxic chemotherapy, preferably anthracycline-based as consolidation. This combined approach results in long-term DFS in 60–70% of newly diagnosed PML patients [21].

Approximately 10% to 20% of patients with PML died before or either during chemotherapy of bleeding attributable to disseminated intravascular coagulation, fibrinolysis and proteolysis [24]. Because ATRA differentiates leukemic promyelocytes into mature cells, one of the major effects of its administration in patients with PML is the reduction in early mortality due to the abrogation of the bleeding diathesis that characterizes this disease [25]. Some studies have shown that the early mortality of patients with PML treated with ATRA as initial therapy diminishes. In the study of Tallman et al. [26], the deaths within 28 days were 14% in patients given ATRA and 11% in those given CT, which contrasts with our data of 4 and 44%, respectively. Also in the study by Tallman et al. [26], the 12-month DFS was 87% and 57%, respectively, for patients treated with either ATRA or combined CT, figures that in our study are also lower—50% and 13%, respectively.

We have previously analyzed some factors that explain the poorer outcomes of treatment of patients with acute leukemia in developing countries [27–31]: specifically in acute myelogenous leukemia (AML), we have shown that the early mortality of these patients in circumstances that are not endowed with adequate blood bank facilities is unacceptably high (36%), stemming from an insufficient platelet transfusion support [28]. This may be one reason to explain the high early mortality in the group of PML patients treated with CT as initial treatment. We have also shown that in our country, and due to different reasons, AML patients treated at University Hospitals obtain less favorable results when compared with AML patients treated at the private practice [28]. Along this line, it should be noted that 3 of 25 (12%) patients in the initial ATRA arm and 4 of 6 patients (66%) in the initial CT arm died in CR during consolidation CT ($P < 0.02$); because all patients in the CT arm were treated at University hospitals, this figure could be biased by the multi-factorial difficulties faced at University hospitals along the anti-leukemic treatments [27–31]. In these PML patients the CR rate in those treated at the private practice (100%), most of them in an outpatient basis [6], was higher than that obtained at University Hospitals, whereas the 5-day mortality was nil: it is possible that PML patients in University hospitals are accepted in worse conditions related with the presence of infections, more advanced stages of the dis-

ease, more severe bleeding complications, etc. [27–31]. The data from this study is novel in that it shows that in developing countries the use of ATRA allows approximately 50% of patients to be treated solely as outpatients and it appears to significantly reduce early mortality compared to use of chemotherapy.

Stemming from the economical restrains in developing countries, we have been interested in developing methods to lower the costs of the hematological treatments: we have shown that both myelosuppressive chemotherapy [18] and peripheral blood stem cell autografts [20] can be delivered and performed safely on an outpatient basis. Because myelosuppression is less marked in PML patients treated with ATRA, we have also been able to deliver this treatment on an outpatient basis in 13 of 27 patients; interestingly, the median age of the patients that were given ATRA on an outpatient basis was not different from that of the whole group. Fundamental to the success of this approach is the availability of a 7 day per week clinic where medications and transfusions can be rapidly and efficiently provided when needed. The outpatient delivery of the ATRA, coupled with the diminished requirement of platelet transfusions stemming from the rapid and effective control of the bleeding diathesis with ATRA [25] likely leads into diminished costs of this antileukemic treatment. Because ATRA was donated for this study, we are unable to compare costs of treatment in both arms; however, we think that final costs of the ATRA arm were lower than those in patients treated initially with combined CT.

In conclusion, we have found that the initial treatment with ATRA of PML patients results in a substantial decrease of the early mortality, and probably in a decrease of the total costs of the anti-leukemic treatment. Because some patients with PML given ATRA as initial therapy can be treated as outpatients, the costs of the treatment may be diminished even more. Studies conducted in other developing countries should be useful to analyze if this initial observation can also be applied under other circumstances.

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REFERENCES

1. Kakizuka A, Miller WH, Umesono K, Warrel RP, Frankel SR, Murty VVVS, Dmitrovsky E, Evans RM. Chromosomal translocation t (15;17) in acute promyelocytic leukemia fuses RAR-alpha with a novel putative transcription factor PML. Cell 1991;66:663.
2. De Thé, Lavau C, Marchio A, Chomienne C, Lanotte M, Degos L, Dejean A. The PML/RAR-alpha fusion mRNA generated by the t (15;17) translocation in acute promyelocytic leukemia encodes a functionally altered RAR. Cell 1991;66:675.
3. Turhan AG, Lemoine FM, Debert C, Bonnet ML, Baillou C, Picard F, Macintyre EA, Varet B. Highly purified primitive hematopoietic stem cells are PML/RAR-alpha negative and generate nonclonal progenitors in acute promyelocytic leukemia. Blood 1995;85:2154–2161.
4. Ruiz-Argüelles GJ, Garcés-Eisele J, Ruiz-Argüelles A. Continued complete remission after a PML/RAR-α positive autograft in acute promyelocytic leukemia. Eur J Haematol 1996;56:186–187.
5. Miller WJR, Kakizuka A, Frankel SR. Reverse transcription polymerase chain reaction for the rearranged retinoic acid receptor alpha clarifies diagnosis and detects minimal residual disease in acute promyelocytic leukemia. Proc Natl Acad Sci USA 1992;89:2694.
6. Ruiz-Argüelles GJ, Garcés-Eisele J, Ruiz-Argüelles A. Molecular follow-up of patients with promyelocytic leukaemia treated with all trans-retinoic acid. Clin Lab Haematol 1998;20:173–176.
7. Miller WH, Levine K, deBlasio A, Frankel SR, Dmitrovsky E, Warrel RP Jr. Detection of minimal residual disease un acute promyelocytic leukemia by a reverse transcription polymerase chain reaction assay for the PML 7 RAR-alpha fusion mRNA. Blood 1993;82:1689–1694.
8. Grignani F, Fagioli M, Alcalay M, Longo L, Pandolfi PP, Donti E, Biondi A, Lo Coco F, Grignani F, Pelicci PG. Acute promyelocytic leukemia: from genetics to treatment. Blood 1994;83:10–25.
9. Ruiz-Argüelles GJ, Ruiz-Argüelles A, Pérez-Romano B, Marín-López A, Larregina-Díez A, Apreza-Molina MG. Filgrastim-mobilized peripheral blood stem cells can be stored at 4 degrees and used in autografts to rescue high-dose chemotherapy. Am J Hematol 1995;48:100–103.
10. Ruiz-Argüelles GJ. Promyelocytic leukemia in Mexican mestizos. Blood 1997;89:348–349.
11. Ruiz-Argüelles GJ, Gómez-Almaguer D, Delgado-Lamas JL, Mejía Domínguez AM, Gil-Rondero C, Almaguer-Gaona C, Apreza-Molina MG. High frequency of acute promyelocyitic leukemia in Mexican Mestizos. A multicenter study. Br J Haematol 1998;102(Suppl 1):37.
12. Rubio-Borja ME, Ovilla-Martínez R, Labardini J, Gómez-Almaguer D, Ruiz-Argüelles GJ, Gómez-Morales E, Borbolla R. All-trans retinoic acid (ATRA) for acute promyelocytic leukemia (APL): Toxicity and survival in de novo patients. Blood 1994;84(Suppl 1):147a.
13. Ruiz-Argüelles GJ, McArthur J. Leucemias agudas. In: Ruiz-Argüelles GJ, editor. Fundamentos de hematología. 2nd edition. México City: Editorial Médica Panamericana; 1998. p 180–197.
14. San-Miguel JF, Duque R. Utilidad del inmunofenotipo en el diagnóstico y clasificación de las leucemias agudas. In: Ruiz-Argüelles GJ, San-Miguel JF, editors. Actualización en leucemias. México City: Editorial Médica Panamericana; 1996. p 25–34.
15. Ruiz-Argüelles A. Flow cytometry in the clinical laboratory. Principles, applications and problems. Ann Biol Clin 1992;50:735–743.
16. Ruiz-Argüelles A, Duque RE, Orfao A. Report of the first Latin American consensus conference for flow cytometric immunophenotyping of leukemia. Cytometry (Communications in Clinical Cytometry) 1998;34:39–42.
17. Biondi A, Rambaldi A, Pandolfi PP, Rossi V, Giudici G, Alcalay M, LeCoco F, Diverio D, Pagliani EM, Lanzi EM, Mandelli F, Masera G, Barbui T, Pellici PG. Molecular monitoring of the myl/retinoic acid receptor alpha fusion gene in acute promyelocytic leukemia by polymerase chain reaction. Blood 1992;80:492–497.
18. Ruiz-Argüelles GJ, Apreza-Molina MG, Alemán-Hoey DD, Gómez-Almaguer D, Marín-López A, Mercado-Díaz L. Outpatient supportive therapy after induction to remission therapy in adult acute myelogenous leukaemia (AML) is feasible: A multicentre study. Eur J Haematol 1995;54:18–20.
19. Ruiz-Argüelles GJ, Ruiz-Argüelles A, Pérez-Romano B, Marín-López A, Delgado-Lamas JL. Non-cryopreserved peripheral blood stem cells autotransplants for hematological malignancies can be performed entirely on an outpatient basis. Am J Hematol 1998;58:161–164.

20. Kaplan EL, Meier P. Nonparametric estimations from incomplete observations. J Am Stat Assoc 1958;53:457–463.
21. Warrel RP Jr. Pathogenesis and management of acute promyelocytic leukemia. Annu Rev Med 1996;47:555–565.
22. Huang ME, Ye YC, Chen SR. All-trans retinoic acid with or without low dose cytosine arabinoside in acute promyelocytic leukemia. Report of 6 cases. Chin Med J 1987;100:949–953.
23. Warrel RP Jr, Maslak P, Eardley A. Treatment of acute promyelocytic leukemia with ATRA: an update of the New York experience. Leukemia 1994;8:929–933.
24. Tallman MS, Kwaan HC. Reassesing the hemostatic disorder associated with acute promyelocytic leukemia. Blood 1992;79:453–553.
25. Barbui T, Finazzi G, Falanga A. The impact of all-trans retinoic acid on the coagulopathy of acute promyelocytic leukemia. Blood 1998;91: 3093:3102.
26. Tallman MS, Andersen JW, Schiffer CA, Appelbaum FR, Feusner JH, Ogden A, Sheperd L, Willman C, Bloomfield CD, Rowe JM, Wiernik PH. All-trans-retinoic acid in acute promyelocytic leukemia. N Engl J Med 1997;337:1021–1028.
27. Ruiz-Argüelles GJ. En el tratamiento de leucemia aguda se obtienen resultados tan buenos como en los países desarrollados; sin embargo. Rev Invest Clin Méx 42;161–163:1990.
28. Lobato-Mendizábal E, Ruiz-Argüelles GJ, Ganci-Cerrud G, Gómez-Almaguer D, Lozano de la Vega A, Labardini-Mendez J. Tratamiento a largo plazo y factores pronósticos en leucemia aguda mieloblástica del adulto. Experiencia del grupo INNSZ (Puebla-Monterrey-México). Rev Invest Clin Méx 43:215–222;1991.
29. Lobato-Mendizábal E, Ruiz-Argüelles GJ. Problemas en el tratamiento de las hemopatías malignas en Iberoamérica. In: López-Borrasca A, editor. Enciclopedia de hematología Iberoamericana. Salamanca, Spain: Editorial Universidad de Salamanca; 1992. p 662–666.
30. Lobato-Mendizábal E, Ruiz-Argüelles GJ. Problemas especiales en el tratamiento de las leucemias agudas. In: Ruiz-Argüelles GJ, editor. Temas de medicina interna: Leucemias agudas. México City: Editorial Interamericana; 1993. p 187–192.
31. Ruiz-Argüelles GJ, Ruiz-Reyes G. El tratamiento de las leucemias en países en desarrollo. In: Ruiz-Argüelles GJ, San-Miguel JF, editors. Actualización en leucemias. México City: Editorial Médica Panamericana; 1996. p 147–151.